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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/573,821

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Kazuaki Okuno

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EXAMINER

SWOPE, SHERIDAN

ART UNIT

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1652

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/573,821	Applicant(s) OKUNO ET AL.	
	Examiner SHERIDAN SWOPE	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 April 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-35 is/are pending in the application.
- 4a) Of the above claim(s) 1-11, 13, 14, 17-22, 24, 25 and 28-35 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12, 15, 16, 23, 26 and 27 is/are rejected.
- 7) ☒ Claim(s) 12, 15, 16, 23, 26, and 27 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☒ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>0306:1107</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants' election, with traverse, of OmpT⁹⁷Met and the cleavage motif of SEQ ID NO: 12 in their response of April 3, 2009 is acknowledged. The elected invention is directed to a method for cleaving a polypeptide comprising the cleavage motif of SEQ ID NO: 12 using OmpT⁹⁷Met.

Applicants' traversal is based on the following arguments.

(A) All the independent claims, claims 1, 8, 12-17, and 23 are novel over the cited art. The Office alleges that the claims do not define a contribution over the prior art, because the cleavage site disclosed in Table 3 of Okuno, which has the sequence RLELYK+RHHG, anticipates claim 1. The Office must have meant the sequence ELRLYK+RHHG, which is the one actually disclosed in Table 3 of Okuno. Okuno's cleavage site, however, does not anticipate claim 1. Among other things, claim 1 recites that "a single basic amino acid is not situated at the P6 or P4 position." By contrast, P4 in the sequence ELRLYK+RHHG in Okuno is R (i.e., arginine), which is a basic amino acid.

(B) Finding a lack of unity in dependent claims is improper without a careful consideration of whether the independent claims avoid the prior art.

(C) The species recited in the various Markush groups possess the same or corresponding special technical features as defined in PCT Rule 13.2.

(D) The Markush claims reciting species of cleavage sites have unity of invention.

(E) The Markush claims reciting species of proteases have unity of invention.

Said arguments are not found to be persuasive for the following reasons.

(A) Reply: Applicants' argument is acknowledged. Nonetheless, Okuno et al, 2002 teaches cleavage of the peptide ELELYK[↓]RHHG with OmpT protease (Table 3), wherein a single basic amino acid is not situated at the P6 or P4 position. Okuno et al also teaches cleavage of a

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fusion protein, PRR4A, at the site ...GYDAELALYR[↓]RHHG... (Fig 1A; pg 82, parg 5), wherein a single basic amino acid is not situated at the P6 or P4 position. Said teachings of Okuno et al anticipate Claim 1 and, thus, the species share no special technical feature as defined by PCT Rule 13.2, because the invention, as a whole, does not define a contribution over the prior art.

(B) Reply: See (A), above.

(C) Reply: See (A), above.

(D) Reply: Assessment of Unity of Invention is based on the invention as a whole. A subset of claims cannot have Unity of Invention.

(E) Reply: See (D), above.

The restriction requirement is still deemed proper and is therefore made FINAL.

Claims 1-35 are pending. Claims 1-11, 13, 14, 17-22, 24, 25, and 28-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 12, 15, 16, 23, 26, and 27 are hereby examined.

Priority

The priority date granted for the instant invention is September 29, 2004, the filing date of PCT/JP04/14704, which disclosed the elected invention. If Applicants wish the examiner to consider JP 2003-342183, filed September 20, 2003, an English translation should be filed.

Information Disclosure Statement

Some references listed on the Information Disclosure Statement filed November 15, 2007 have not been considered because they have not been provided to the Examiner (see strikeouts). If Applicants wish for said references to be considered, a supplementary Information Disclosure

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Statement and the references should be filed. Any rejection based on said references will not be considered to be new grounds for rejection.

Claims-Objections

Claims 12, 15, 16, 23, 26, and 27 are objected to for reciting non-elected subject matter.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Utility

Claims 12, 15, 16, 23, 26, and 27 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 15, 16, 23, 26, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

Claims 12, 15, 16, 23, 26, and 27 provides for the use of OmpT⁹⁷Met for cleaving a protein; but, since the claims do not set forth any steps involved in the method/process, it is unclear what

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method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

For Claims 12, 15, 16, 23, 26, and 27, the phrase “OmpT protease” renders the claim indefinite. The specification states that said phrase encompasses any protein having OmpT protease activity and provides four examples [0035]. Based on said statement, the skilled artisan would not know the metes and bounds of the recited invention.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 12, 15, 16, 23, 26, and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cleaving a fusion protein at the C-terminal residue of SEQ ID NO: 12 by isolated E. coli OmpT (Example 8), does not reasonably provide enablement for cleavage of any polypeptide by any “OmpT” variant having a substitution at residue 97. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the

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amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 12, 15, 16, 23, and 27 are so broad as to encompass any method for cleaving any protein using an OmpT variant having a substitution at residue 97. Claim 26 is so broad as to encompass any method for cleaving any protein comprising SEQ ID NO: 12 using an OmpT variant having a substitution at residue 97. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in an OmpT protein's amino acid sequence and obtain the desired cleavage activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to cleaving a fusion protein at the C-terminal residue of SEQ ID NO: 12 by OmpT (Example 8).

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galye et al, 1993; Whisstock et al,

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2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 12, 15, 16, 23, and 27, which encompasses all methods for cleaving any protein using an OmpT variant having a substitution at residue 97. The specification does not support the broad scope of Claim 26, which encompasses all methods for cleaving any protein comprising SEQ ID NO: 12 using an OmpT variant having a substitution at residue 97. The specification does not support the broad scope of Claims 12, 15, 16, 23, 26, and 27 because the specification does not establish: (A) the structural and functional metes and bounds of any “OmpT” protein; (B) all proteins that can be cleaved by the encompassed OmpT variants having a substitution at residue 97; (C) any protein comprising SEQ ID NO: 12 that can be cleaved using an OmpT variant having a substitution at residue 97; (D) regions of the OmpT protein structure which may, or may not, be modified without affecting the desired activity; (E) the general tolerance of the desired activity to modification of OmpT and extent of such tolerance; (F) a rational and predictable scheme for identifying, without undue experimentation, which motifs can be cleaved by all encompassed OmpT variants having a substitution at residue 97; and (G) the specification provides insufficient guidance as to which of the essentially infinite possible choices of combinations of OmpT variants and motifs is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any method for cleavage of any polypeptide by any encompassed OmpT variant having a substitution at residue 97. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of methods having the desired biological

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characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Written Description

Claims 12, 15, 16, 23, and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 12, 15, 16, 23, and 27 are directed to a genus of methods for cleaving any protein using an OmpT variant having a substitution at residue 97. The specification teaches only a few representative species of such methods. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a method for cleaving any protein using an OmpT variant having a substitution at residue 97. Given this lack of description of representative species encompassed by the genera of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim 26 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 26 is directed to a genus of methods for cleaving any protein comprising SEQ ID NO: 12 using an OmpT variant having a substitution at residue 97. The specification teaches no such methods. Given this lack of description of representative species encompassed by the genera of the claims, the specification fails to sufficiently describe the claimed invention in such

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full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Allowable Subject Matter

No claims are allowable.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that the serial number of the application and date of amendment be referenced on every page of the response.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system,

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see <http://pair-direct.uspto.gov>. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652